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THE TRUE FUNCTION OF THE THYMUS.

THERE is hardly an organ in the body about whose functions in the embryo and at later periods so little is really established as the thymus. Since Kölliker[1] discovered its mode of origin in mammals from the epithelium of a gill-pouch and since he stated that the original epithelial cells gave rise to lymph-cells or leucocytes two views have been held concerning it. On the one hand, Stieda[2] and His[3] have maintained that the leucocytes which always form integral parts of the thymus soon after its first origin have migrated thither from the exterior, possibly from the mesoblast. In this conclusion they have been supported by the researches of Dohrn,[4] Gulland,[5] and Maurer,[6] and by almost every text-book of embryology and comparative anatomy published since 1879. On the other hand, Kölliker has stoutly maintained his original position and the results of his investigations have in recent years been emphatically confirmed by Prenant,[7] Oscar Schultze,[8] and myself.[9] According to the views of Stieda and His, Hassall's concentric corpuscles are supposed to arise from the original epithelial cells and the function of the thymus is still absolutely unknown. No serious attempt has ever been made to convert this hypothetical origin of the concentric corpuscles into fact by systematic investigation. On this view, then, nothing of the least practical use and value is at present known regarding the nature of the thymus. According to Kölliker the original epithelial cells of the thymus give rise to lymph cells or leucocytes. And although he made no attempt to explain Hassall's corpuscles it must be evident that, if his conclusion be correct, something of positive value is thereby established. As already stated, the three most recent students of the thymus have entirely accepted Kölliker's results. None the less in the latest English edition (1897) of Wiedersheim's "Comparative Anatomy" the author felt himself obliged to say: "The function of this organ, though doubtless a very important one, is not understood."

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[1] Entwicklungs-geschichte des Menschen und der höheren Thiere, 1879, pp. 875 to 880.

[2] Untersuchungen über die Entwickelung der Glandula, Thymus, &c., Leipsic, 1881.

[3] Anatomie Menschlicher Embryonen, 1880, p. 56.

[4] Mittheilungen aus der Zoologischen Station zu Neapel, 1884.

[5] Reports of the Royal College of Physicians of Edinburgh, 1891.

[6] Morphologisches Jahrbuch, Band xi., 1885.

[7] Développement du Thymus—La Cellule, Tome x., 1894.

[8] Grundriss der Entwicklungs-geschichte des Menschen, &c., 1897.

[9] The Development and Probable Function of the Thymus, Anatomischer Anzeiger, Band ix., 1894.

I have long suspected the function of the thymus to be a very important one but, in spite of repeated attacks on the problem, my researches had until last summer yielded little or nothing beyond a confirmation of Kölliker's brilliant discovery. Even now, when success has completely crowned the failures of past years, at a time when the developmental history and function of the thymus in one vertebrate animal (*Raia batis*, the smooth skate) can be demonstrated on numerous preparations with the utmost certainty and ease, the problem owes its solution in the first instance not to direct attack on the organ itself, but to the unravelling of another puzzle. While engaged on general developmental researches a little, but significant, fact forced itself into notice. This was that for a relatively long period of the development the blood contained only nucleated coloured corpuscles and no leucocytes whatsoever. It was recalled that this had originally been noted by Kölliker some years ago and that it had been commented upon by H. E. Ziegler who had ventured the conjecture—a very safe one—that the condition persisted until some lymphoid organ or other arose. The question was asked, "At what period of the development and from what source or sources do the white corpuscles of the blood or leucocytes arise?" It had previously been recognised that there was a particular epoch of the development, termed by me[10] the "critical period," at which the foundation of every organ of the body was present as such. It was obvious that, if the existence of a critical period had a groundwork of fact, the leucocytes of the blood, as forming integral parts of a vertebrate animal, ought to be present at the critical period, or, if not themselves evident as such, the foundation or foundations from which they arose ought to be in existence. In the fishes studied it was very easily made out that abundant leucocytes were present in the blood at and even before the critical period. Working to earlier stages from this point and from early stages where no leucocytes existed anywhere in the embryos the period was at length reached when leucocytes first entered the scene. When this point had been approximately fixed a dilemma was the first result. For the moment the observer had not the slightest idea whence they came. Kölliker's results on the thymus, proving that it produced leucocytes, were remembered, as was also my own confirmation of them.

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[10] Vide Certain Problems of Vertebrate Embryology, Jena, 1896, and The Span of Gestation and the Cause of Birth, Jena, 1897, both published by Gustav Fischer.

The phase at which leucocytes appeared did not lend colour to the idea that the thymus could have much to do with the matter. For it was recalled that in such embryos the thymus elements (of which there are in the skate five on each side of the body) were then nothing more than small pieces of modified epithelium. Although the thymus was not *a priori* a very promising subject for new research there seemed to be none more likely. At the period when leucocytes first appeared the spleen had no existence, there was no rectal gland or cæcum, and, in fact, lymphoid structures of any and every sort were entirely wanting. As a working hypothesis it was suggested that the first leucocytes of the body were formed by and from the epithelial cells of the thymus. The subsequent investigation of a very extensive series of embryos of the skate fully confirmed this hypothesis and converted it into a fact capable of complete and convincing demonstration in this animal. My results at present relate only to one vertebrate animal and this a fish, *Raia batis*, the smooth skate. None the less, what seem to me to be convincing reasons can be given for extending these to all true vertebrata and to man himself. The plan of the organisation of a skate is practically the same as that of the organisation of man himself. No organ is found in man which has not in some form or other its counterpart in the skate, and the functions of the organs of a man are to all intents and purposes the same as those of like organs in the skate. With the single exception that Hassall's corpuscles have never yet been found in the skate, though not for want of the search for them, the place of origin, the mode of development, and the minute anatomy of the thymus of man essentially agree with those of the same organ in the skate. I have before me as I write sections through the thymus of a late and nearly ripe fœtal rabbit and of a young skate almost ready to leave the egg. In both the main feature of the thymus is the crowd of leucocytes filling the field of the microscope. An experienced embryologist or histologist could not distinguish the one from the other, unless he had previously studied both, knowing what they were. The sole difference is one of size of the leucocytes. Indeed, whether viewed from the standpoint of histology or from that of development there cannot exist the slightest doubt as to the identity of function and structure in the thymus of the skate and of man.

This is not the place in which to give a full and complete record of the research along with the necessary figures. It may suffice to state briefly the results without producing the whole of the evidence on which they are based. The evidences will be given in full in a special memoir, and I would here only ask permission to state that in a working experience of upwards of sixteen years in vertebrate embryology I am aware of no fact which can be so completely and convincingly demonstrated as this origin of the first leucocytes of the body from the cells of the thymus-epithelium. Numerous figures—upwards of forty—have already been carefully drawn, and even fifty times this number would not exhaust all the preparations at my disposal. Many of the figures have been drawn under a $\frac{1}{18}$ oil-immersion of Leitz, and but for the use of such a high lens as this some of the results could not have been obtained.

The thymus of the skate is certainly hypoblastic in origin, and the plate of epithelial cells (of one layer of cells) which gives rise to any one of the ten thymus elements of *Raia*, can be made out before any of the gill-pouches are open to the exterior. It then forms in each pouch a well-defined portion of the dorsal wall. After rupture of the pouch it is pushed somewhat upwards and outwards and ultimately comes to lie on the level of the notochord. Afterwards by increase among its cells the one-layered arrangement is converted into a formation of two or three cells deep. The mode in which the epithelial cells become converted into leucocytes can be readily observed under high magnifications in sections of embryos of 17 to 22 mm. Without describing the details at length it may be stated that the process is exactly comparable to that in which the original epithelial cells of the brain or spinal cord become converted into ganglion cells. Being now thoroughly familiar with the development of both ganglion-cells and leucocytes I have no hesitation in making this statement. As in the development of ganglion cells the original parent-cells of leucocytes are epithelial cells. To study the conversion of these into leucocytes one needs to examine the parent-epithelium of the thymus under very high lenses. For this purpose the lens made use of has been a $\frac{1}{18}$ oil-immersion of Leitz. The first change in such an epithelial cell appears to be one in its protoplasm or cytoplasm. This becomes somewhat more refractive and in favourable sections takes on a somewhat brownish tinge. At first no alteration can be noticed in the nucleus which is oval as in the other epithelial cells. Then the nucleus becomes rounded and gradually the whole cell acquires this shape. With this and the marked refractile nature of the protoplasm the cell has taken on the characters of a leucocyte. Another peculiarity, already recorded by M. Heidenhain regarding leucocytes, is that the nucleus comes to occupy an excentric position. Many of the earliest-formed leucocytes apparently remain, at any rate for a time, within the epithelium, while others of them proceed to wander out into the mesoblast and elsewhere. Those that remain seem to undergo division, for only in this way can the numerous cell nests of them and little groups of twos and fours be explained. Those which wander out may be caught in the act of emigration and there, are several drawings of preparations showing leucocytes in the act of emerging singly from the epithelium. They are not wandering into the epithelium, for until some are formed within the latter there is no source in the body whence they could be derived. Neither do they enter it as epithelial or connective cells or as "mesenchyma," for there are no evidences whatever of this. In fine, in early stages all the evidence goes to prove the gradual conversion of the epithelial cells of the thymus-epithelium into leucocytes, Stieda asks in his work on the Thymus, &c., "How can adenoid tissue arise from an epithelium?" The difficulty of understanding this may have existed in 1881 when there were hardly any observations whatever concerning the origin of lymphoid cells. There is no longer any difficulty about the matter when many convincing preparations can be produced to show it. Where nature raises no obstacle in the way of carrying out a process it is not for man to invent one.

The fact is that in nature, as Kölliker stated in 1879 and as my preparations enable me to prove, adenoid tissue does arise from epithelial cells. In embryos of 22 mm. in length and smaller the production of leucocytes is not great. In a single section of one thymus element one may in such embryos count from six to a dozen cells which are either fully-formed leucocytes or are taking on leucocytic characters. Only rarely is the emigration of a single leucocyte observed, there are few in the mesoblast near the thymus and in the blood itself. In embryos of 25 mm. progress is being made. Leucocytes and leucocytic cells are far more numerous within the epithelium, from twenty to thirty being met with in a single transverse section. Their emigration is now a more conspicuous phenomenon. One may still meet with single leucocytes caught in the act of emigrating, but this has begun to give place to a slightly different process to be presently described. As Kölliker first stated, for a period of some duration the embryonic blood is destitute of leucocytes and this is true of the embryonic blood of all vertebrates from fishes to man. My researches have revealed the fact that this absence of leucocytes obtains until the first ones are formed within the thymus-epithelium and from its epithelial cells.

As soon as leucocytes begin to be formed in the early history of the thymus some of these wandering cells, true to their hereditary instincts, begin to emigrate singly from the thymus, making their way into the mesoblast, and sooner or later, very soon to all appearances, many of them also get into the blood. The emigration of single leucocytes only goes on as long as their production is not great. When the thymus elements set to work in earnest to form leucocytes—i.e., in embryos of 28 mm. and upwards—they emerge from the thymus in crowds, thus causing larger or smaller "breaks" at various places on its contour. These "breaks" are found in almost every section of every thymus element of every embryo between the sizes of 28 mm. and 42 mm. Taking only 10 such embryos from my collection, the actual number being really about 20, as there are 10 thymus elements, 5 on each side, in each embryo, and as the number of sections through each of these elements will be from 10 to 20, it is not an exaggeration to estimate that there are hundreds of sections all showing these breaks and the emigration of leucocytes from the thymus. In this way the whole body of the embryo, including its blood, soon becomes richly infiltrated with leucocytes. This happens before lymphoid structures are developed elsewhere within the body and demonstrably these first leucocytes of the blood and of the body have taken their origin in one or other of the ten thymus elements of *Raia*. A capsule of connective tissue and blood capillaries is formed very late

(43 to 54 mm. embryos) and from this period the majority of the leucocytes produced by the thymus probably make their way directly into its capillaries. Hassall's concentric corpuscles have not been met with at any period in the thymus of *Raia*. It is, of course, quite possible that they may be found in old skates; but, as these animals possess no certificate of birth, the search for such an example might not be successful.

Before indicating the conclusions to be drawn from these results it is fitting that the services of my predecessors should receive proper notice. The claims of other workers on the thymus would be set forth at length with the necessary quotations from their works and in their own words in a more extended memoir. The history of the histogenesis of the thymus—and a sad one it is—begins with the researches of Kölliker published in 1879. In these Kölliker stated that the thymus of the rabbit arose from (the wall of) a gill-cleft and that its original epithelial cells became converted into leucocytes. This latter discovery is among the most brilliant ever made by the honoured Nestor who has occupied a pre-eminent position in the embryological and histological research of the past fifty years. But its fate has been the very reverse of that to which its importance in embryology, histology, physiology, pathology, and practical medicine fully entitled it. Against his results were placed the conjectures and assertions of Stieda and His, and although these never obtained a really satisfactory basis of support in the researches of the two anatomists just named or of others, although they were never really based on actual "finds" at all, they sufficed to dominate our ideas as to the nature of the thymus for nearly twenty years. According to them leucocytes wandered into the thymus from the mesoblast and the original epithelial cells of the thymus gave rise to Hassall's corpuscles.

Now, in the skate, as we have seen, Hassall's corpuscles have not yet been found and the original epithelial cells give rise to leucocytes, as is now abundantly proved for this and several other vertebrates, fishes and mammals, by the researches of Kölliker, Maurer (in part), Prenant, Oscar Schultze, and myself. Moreover, how can leucocytes wander into the thymus from the mesoblast or from any other part of the embryonic body at a period when there are none in existence elsewhere? How can this happen when the very first source of leucocytes in the body is the epithelium of the thymus itself? The formation of leucocytes is, therefore, as

Kölliker first showed, a function of the thymus. But as my researches prove, one can now go on a good deal further, and state with the utmost confidence that it is the function of the thymus not merely to form leucocytes, but to be the parent source of all the leucocytes of the body.

In 1891 Gulland stated that the first leucocytes of the body arose in the mesoblast in the neighbourhood of the thymus. One cannot help wondering whether or not he put the further question to himself, "Whence do they come?" At any rate, he gave no correct answer to the query, and the first reply to it is contained in the present communication. It is Kölliker's great service to have shown that leucocytes arise in the thymus from its original epithelial cells; to Gulland's researches we owe the result that the first leucocytes are found in the mesoblast in the neighbourhood of the thymus; and, finally, it has fallen to my lot to show that the *first leucocytes arise in the thymus from its epithelial cells, and that thus it is the parent source of the leucocytes of the body.* The last link of the chain binding the whole together has now at length been forged, and that this is so may be shown in another way. Is there any other probable source of leucocytes in the vertebrate body? The answer to this question must now be a most decided negative, and this for the following reasons.

1. When the first leucocytes arise in the thymus-epithelium there are no leucocytes and no lymphoid structures of any sort in any other part of the body. The first or parent leucocytes by their wanderings quickly infiltrate the blood and most other parts of the body. From this it follows that if a lymphoid organ arises later elsewhere it will always be impossible to prove that it did not take its origin from some of the leucocytes or their progeny which originally came from the thymus. If a new outbreak of an infectious disease occur in a street at a time when in another part of the street the same illness has already manifested itself, the latter or its original source is considered sufficient to account for the fresh cases. The white races of America are descended from ancestors who emigrated from Europe and no one would dream of enunciating the idea that the white inhabitants of, say, a western prairie village had arisen *de novo in loco.*

2. No other lymphoid organ is known which in its developmental history resembles the thymus. Attempts have been

made by Retterer and others to prove such a mode of origin of lymphoid structures in the case of the tonsils, parts of the alimentary canal, and the bursa Fabricii of birds, but these have all one after the other been disproved by an able embryologist and histologist, Professor Philip Stöhr.

3. The thymus alone is sufficient to account for all the leucocytes of the body, and since Schaffer demonstrated its existence in Marsipobranchiate fishes—a discovery which I can confirm—we now know it to be an organ characteristic of all true vertebrate animals.

4. Except in the case of organs which are paired or form parts of a metameric segmentation, we do not seek for two organs with the same function in any vertebrate animal. The thymus is a paired, metamerically repeated organ if the gill-region be metameric, but its development is confined to that region in all known cases.

In the trunk-region of no vertebrate is the homologue of any organ occurring in its branchial region encountered. It must, therefore, be held—and in my humble opinion the contrary is impossible of proof—that the thymus is the parent-source of all the lymphoid structures of the body. This conclusion throws light upon one of the teachings of embryologists, histologists, and pathologists—that the thymus is an example of an organ which after assuming function in early life atrophies at a later period. This is only certainly known to happen in mammals, and from it the inference is drawn that in later life the organ ceases to exist. It no more ceases to exist than would the Anglo-Saxon race disappear if the British Isles sank beneath the waves. The simile is a real one, for just as the Anglo-Saxon stock has made its way from its original home into all parts of the world and has there set up colonies for itself and for its increase, so the original leucocytes, starting from their birthplace and home in the thymus, have penetrated into almost every part of the body and have there created new centres for growth, for increase, and for useful work for themselves and for the body.

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